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INTERNATIONAL PRELIMINARY EXAMINATION REPORT  
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 29312-0180		<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/CA 03/00066	International filing date (day/month/year) 21.01.2003	Priority date (day/month/year) 21.01.2002	
International Patent Classification (IPC) or both national classification and IPC A61K47/48			
Applicant VASOGEN IRELAND LIMITED et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
  - ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:
  - I ☒ Basis of the opinion
  - II ☐ Priority
  - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV ☐ Lack of unity of invention
  - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI ☐ Certain documents cited
  - VII ☐ Certain defects in the international application
  - VIII ☐ Certain observations on the international application

Date of submission of the demand  19.08.2003	Date of completion of this report  10.05.2004
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer  Vermeulen, S Telephone No. +49 89 2399-7520 

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA 03/00066

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

### Description, Pages

1, 3-15 as originally filed  
2, 2a filed with telefax on 15.04.2004

### Claims, Numbers

1-19 filed with telefax on 15.04.2004

### Drawings, Figures

1-2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

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5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**see separate sheet**

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 19

because:

☒ the said international application, or the said claims Nos. 19 relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-19
	No: Claims	none
Inventive step (IS)	Yes: Claims	none
	No: Claims	1-19
Industrial applicability (IA)	Yes: Claims	1-18
	No: Claims	19 (no opinion)

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2. Citations and explanations  
**see separate sheet**

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**Re Item I**

**Basis of the report**

The amended claim 1 filed with the fax dated 10 December 2003 introduces subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT:

For the more general RGD peptide no amounts of bodies to be comprised in a unit dosage are disclosed in the application as originally filed. The indication of an amount of 500 to  $2.5 \times 10^9$  bodies comprised in a unit dosage is only disclosed for the peptide sequence RGDS (cf. page 8).

Accordingly, the present preliminary examination report has been made on the basis of claim 1 wherein the RGD sequence is defined as RGDS.

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claim 19 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Reference is made to the following documents:

- D1: US-A-5 840 691 (EVERETT JEFFREY E ET AL) 24 November 1998
- D2: LESTINI B J ET AL: 'Surface modification of liposomes for selective cell targeting in cardiovascular drug delivery', JOURNAL OF CONTROLLED RELEASE, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL, VOL. 78, NR. 1-3, PAGE(S) 235-247 XP004329821 ISSN: 0168-3659
- D3: SJAASTAD MICHAEL D ET AL: 'Feedback regulation of cell-substratum adhesion by

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integrin-mediated intracellular Ca-2+ signaling.' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 91, no. 17, 1994, pages 8214-8218, XP002245778 1994 ISSN: 0027-8424

D4: ADDERLEY SHARON R ET AL: 'Glycoprotein IIb/IIIa antagonists induce apoptosis in rat cardiomyocytes by caspase-3 activation.' JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 275, no. 8, 25 February 2000, pages 5760-5766, XP002245779, cited in the application

D5: EP-A-0 298 820 (INST NAT SANTE RECH MED ;LAFON LABOR (FR)) 11 January 1989

D6: PATENT ABSTRACTS OF JAPAN & JP 08 183740 A (NIPPON STEEL CHEM CO LTD), 16 July 1996

D7: ITO M ET AL: 'T cell adherence and mucosal injury in ulcerative colitis: involvement of integrin-fibronectin interaction in situ.' JOURNAL OF GASTROENTEROLOGY. JAPAN NOV 1995, vol. 30 Suppl 8, November 1995, pages 70-72, XP009012797

2. The use and the method as defined in the independent claims 1 and 19 may be regarded as novel insofar as the state of the art represented by D1-D7 does not unambiguously disclose the use and administration of a unit dosage form comprising from about 500 to about  $2.5 \times 10^9$  RGDS carrying bodies. In comparison, the prior art documents D1 (column 10, lines 7-16), D2 (page 239, paragraph 2.5.) and D5 (page 8, lines 8-10) express doses of the peptide carrying bodies in weight amounts.
3. The subject-matter of independent claims 1 and 19 is however not considered to involve an inventive step (Art. 33(3) PCT) for the following reasons: The claimed subject-matter differs from e.g. D1 only in that the dosage is defined as a number amount of peptide carrying bodies, whereas D1 defines a weight amount of peptide carrying bodies. The bodies according to claims 1 and 19 may have a size of up to 500  $\mu\text{m}$  and being comprised in an amount of up to  $2.5 \times 10^9$  bodies per unit dosage. Insofar as claims 1 and 19 do not contain any indication on the weight range of the individual peptide carrying bodies, the expression of the dosage as a number amount is considered merely an obvious alternative to the dosage expressed as a weight amount according to D1. The suggested dosage in D1 ranges from 1 to 100 mg/kg/day for adult humans, however, lower or higher amounts may be more appropriate (cf. column 10, lines 7-16). The RGD carrying bodies according to D1 consist of conjugates of multiple polypeptide fragments bound to a carrier molecule such as ovalbumin, human serum albumin, other proteins, PEG, etc. (cf. column 8, lines 54-67). Hence, bodies of different weight and size are possible alternatives suggested by D1. Accordingly, the unit dosage form taught by D1 and expressed as a weight amount also anticipates any number amount of bodies

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comprised said unit-dosage form.

4. The dependent claims 2-18 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, would render the claimed subject-matter inventive (Art.33(3) PCT). Said features relate to the use of the RGDS-peptide to inhibit or alleviate the (inflammatory) symptoms of diseases or disorders. For the defined diseases and disorders however the beneficial effect of RGDS-peptide sequence has already been reported and its therapeutical use disclosed or at least suggested by D1, D2, D5-D7 (cf. passages cited in ISR).

to those cells of the body that remove apoptotic cells. A number of specific ligands expressed on apoptotic cells have been observed to induce an anti-inflammatory response as a consequence of interaction with receptors, in antigen presenting cells, for example by inducing the down-regulation of certain inflammatory cytokines and/or the up-regulation of certain anti-inflammatory cytokines by antigen presenting cells. There are a number of cell surface ligands which are present either uniquely or at increased levels on apoptotic cells compared to normal cells. These include phosphatidylserine (PS), a phospholipid normally restricted to the inside of the cell membrane but which becomes transferred to the outside of the membrane during apoptosis, and interacts with PS receptors on antigen presenting cells.

The result of the process of interaction of ligands and receptors in the process of apoptotic death of cells in the mammalian body is a change in the cytokine production profile of various cells in the mammalian immune system, especially the antigen presenting cells involved in the uptake of the products of apoptosis.

Peptides containing the integrin recognition motif RGDS (Arg-Gly-Asp-Ser) are known to interact with receptors on antigen-presenting cells.

## WHAT IS CLAIMED IS:

1. A composition of matter capable of producing an anti-inflammatory response *in vivo* in a mammal, said composition comprising bodies selected from liposomes, solid beads, hollow beads and filled beads, capable of being phagocytosed in vivo by mammalian antigen-presenting cells resulting in the alteration of the cytokine profile of cells of the mammalian immune system, having a size from about 20 nanometers to 500 microns in diametric dimension, expressing or expressible on the surface thereof an active group containing the peptide sequence RGD.
2. Composition of matter according to claim 1 comprising a three-dimensional body portions selected from liposomes, solid beads, hollow beads and filled beads.
3. Composition of matter according to claim 2 wherein the active peptide group is RGDS.
4. Use in the preparation of a medicament for alleviating or inhibiting the symptoms of inflammation in a mammalian patient, of synthetic bodies selected from liposomes, solid beads, hollow beads and filled beads, capable of being phagocytosed in vivo by mammalian antigen-presenting cells resulting in the alteration of the cytokine profile of cells of the mammalian immune system, having a size from about 20 nanometers to 500 microns in diametric dimension, expressing or expressible on the surface an active group containing the peptide sequence RGD.
5. Use as in claim 4 wherein the active peptide group is RGDS.

6. Use as in claim 5 for preparation of a medicament for alleviating or inhibiting the symptoms characteristic of a neurodegenerative disease.
7. Use as in claim 6 for preparation of a medicament for alleviating or inhibiting the symptoms characteristic of Parkinson's disease.
8. Use as in claim 6 for preparation of a medicament for alleviating or inhibiting the symptoms characteristic of Alzheimer's disease.
9. Use as in claim 5 for preparation of a medicament for alleviating or inhibiting the symptoms characteristic of a cardiovascular disease.
10. Use as in claim 9 for preparation of a medicament for alleviating or inhibiting the symptoms characteristic of atherosclerosis.
11. Use as in claim 5 for preparation of a medicament for alleviating or inhibiting the symptoms characteristic of an autoimmune disease.
12. Use as in claim 5 for preparation of a medicament for alleviating or inhibiting the symptoms characteristic of an endothelial dysfunction.
13. A process of alleviating or inhibiting the symptoms of inflammation in a mammalian patient, which comprises administering to the patient an effective amount of a composition of matter comprising synthetic bodies having a three-dimensional core structure of size from 20 nanometers to 500 microns expressing or expressible on the surface thereof RGDS ligands which will react, optionally in the presence of adapter molecules, with at least one specific receptor wherein the binding of said ligand with

said receptors produces an anti-inflammatory response *in vivo* in said mammal.